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A CROSS-SECTIONAL INVESTIGATION OF A CONTROLLED TRIAL OF INTRATHECAL ANTIBIOTIC THERAPY IN INFANTS WITH GRAM-NEGATIVE ENTERIC MENINGITIS

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ABSTRACT

Background: Gram-negative enteric meningitis in infants is a excessive and lifestyles-threatening situation because of bacteria which include Escherichia coli, Klebsiella species, and different enteric pathogens. This type of meningitis is specifically hard to treat due to the increasing occurrence of antibiotic-resistant strains and the difficulties in achieving therapeutic concentrations of antibiotics within the cerebrospinal fluid (CSF) due to the blood-mind barrier.

Objective: To assess the effectiveness and safety of the antibiotics administered intrathecally in infants suffering from gram negative enteric meningitis.

Methodology: The study included 100 infants diagnosed with Gram-negative enteric meningitis. The study was conducted at Naseer Teaching Hospital during the period from September 2022 to September 2023. They were then equally divided into two groups i-e intrathecal therapy group and systemic therapy group with 50 participants in each group. Their baseline characteristics including age, sex, birth weight, gestational age, and initial CSF WBC count were recorded. Bacterial degradation was observed at 46 hours, 7 days, and 10 days of treatment.

Results: The intrathecal group showed significantly higher bacterial clearance rates at 46 hours ($p=0.04$), 7 days ($p=0.02$), and 10 days ($p=0.02$). Peak CSF antibody concentrations were raised in the intrathecal therapy ($p = 0.01$), and serum concentrations were also higher ($p = 0.03$). Better outcomes were observed in the intrathecal group ($p=0.03$), with shorter hospital stay ($p=0.001$).

Conclusion: The use of intrathecal antibiotic is an advanced alternative to standard systemic antibiotic therapy for the control of gram-negative enteric meningitis in infants. The superior bacterial clearance, higher CSF antibiotic concentrations, and improved scientific results highlight it as an effective treatment modality.

Keywords: Gram Negative Bacteria, Intrathecal, Meningitis, Antibiotics

INTRODUCTION

Even with the development of new chemotherapy medications and sophisticated medical facilities, infant gram-negative bacillary meningitis still has an unfavourable outcome.(1) This illness has fatalities that vary between 40% to 80%, and the majority of those who survived experience neurologic and developmental issues.(2) When a child reaches age for school, cognition and interaction problems may manifest in individuals who were previously thought to be healthy after recovering from meningitis in childhood.(3)

The main goal of antibiotics for newborn meningitis is to eradicate the illness by obtaining levels of antibiotics in the cerebrospinal fluid (CSF) that are higher than minimum inhibitory concentration (MIC) of the bacterial pathogen.(4) CSF samples should be sterilised as soon as possible when meningitis triggered by gram-positive bacteria, such as group B streptococci, is suspected.(5) This is because the highest CSF levels of ampicillin or penicillin are roughly one hundred times greater compared to the MIC values.(6)

On the other hand, the CSF's peak aminoglycoside levels of antibiotics are about equal to the intestinal bacteria's minimum inhibitory concentrations (MIC).(7) As a result, CSF samples from newborns suffering from enteric meningitis that is gram-negative may continue to be positive for a maximum of five days.(8) An antibiotic treatment that accomplishes a speedy bacteriological recovery is essential because the length of positive CSF cultures significantly impacts the final result of newborn meningitis.(9)

The efficacy of intrathecal treatment with antibiotics for gram-negative bacterial neonatal meningitis was assessed by the Neonatal Meningitis Cooperative Study Group.(10) This method of delivery was chosen because it was thought that injecting a medication right away into the lumbar intrathecal space would promote antimicrobial action across the cerebral spinal fluid (CSF) volume, resulting in a quicker removal of microbes and better illness results.(11) The aim of the present study is to To assess the effectiveness and safety of the antibiotics administered intrathecally in infants suffering from gram negative enteric meningitis.

METHODOLOGY

We conducted cross sectional study in Naseer Teaching Hospital, Peshawar. This study was conducted in 12 months from the time duration of September 2022 to September 2023. The sample size of our study participants was 100 infants diagnosed with gram-negative enteric meningitis. The participants were treated with intrathecal antibiotics versus standard systemic antibiotic therapy. Infants aged 0-12 months diagnosed with gram-negative enteric meningitis, confirmed by positive CSF culture, infants with no prior history of severe allergic reactions to the antibiotics used in the study and those whose parental consent for participation were enrolled in the study. The exclusion criteria involve infants with congenital or acquired immunodeficiency, with significant comorbidities such as severe cardiac, hepatic, or renal dysfunction and with a history of neurosurgical procedures or CSF shunt placement.

Upon diagnosis of gram-negative enteric meningitis, eligible infants were allocated at random to either of the two treatment groups: i-e Intrathecal Antibiotic Therapy Group (IATG) and Standard Systemic Antibiotic Therapy Group (SSATG). The IATG received standard systemic antibiotic therapy plus intrathecal administration of an appropriate antibiotic (based on culture and sensitivity results). And SSATG received standard systemic antibiotic therapy alone.

Data collection included baseline assessment i-e Demographic data, clinical presentation, and initial laboratory findings including CSF analysis. The microbiological evaluation involved serial CSF cultures which were obtained at baseline, 46 hours, 7 days, and 10 days post-treatment initiation to monitor bacterial clearance and the pharmacological monitoring involved serum and CSF antibiotic concentrations which were measured at specified intervals to assess drug penetration and pharmacokinetics. Vital signs, neurological status, and occurrence of any adverse effects were monitored daily. Intrathecal Antibiotic Therapy was administered intrathecally via lumbar puncture at a dose adjusted for the infant's weight and based on pharmacokinetic data to ensure therapeutic CSF

concentrations. Systemic Antibiotic Therapy was administered intravenously according to standard dosing guidelines for neonates, adjusted based on culture and sensitivity results.
Rate of bacterial clearance from the CSF at 7 days post-treatment initiation were our primary outcome and clinical improvement (resolution of symptoms), duration of hospital stay, incidence of adverse effects, and overall survival rate were secondary outcomes.
Data were analysed using SPSS version 26. Descriptive statistics were used to summarize baseline characteristics and treatment outcomes. Chi-square tests were used to compare categorical variables between groups, while t-tests or Mann-Whitney U tests were used for continuous variables, as appropriate. Kaplan-Meier survival analysis was performed to compare time to bacterial clearance among both groups. 'Statistical significance was attained when the p-value was less than 0.05'.
Naseer Teaching Hospital's Institutional Review Board (IRB) gave the study its approval. Written informed consent was obtained from the parents or guardians of all participating infants.

RESULTS

The study involved 100 infants and the mean age in the intrathecal antibiotic therapy group was 3.2 ± 2.2 months, while in the standard systemic antibiotic therapy group it was 3.5 ± 2.4 months ($p = 0.78$) Males and female distribution was similar between the groups, and was 27 males and 23 in the intrathecal group Females were 31 males and 19 in the systemic group ($p = 0.62$) and the mean birth weight was 3.0 ± 0.6 kg in the intrathecal group of the versus 3.1 ± 0.7 kg in the systemic group ($p = 0.63$). Gestational age at delivery was also comparable between the two groups, averaging 38.7 ± 1.3 and 38.6 ± 1.2 weeks, respectively ($p = 0.52$). All participants in both groups had a positive CSF culture at baseline. The initial CSF white blood cell (WBC) count was similar between the groups, with means of 121 ± 49 cells/μL and 116 ± 54 cells/μL ($p = 0.84$). (Table 1)
At 46 hours post-treatment initiation, 71.2% (34/50) of infants in the intrathecal antibiotic therapy group achieved bacterial clearance, compared to 51.3% (24/50) in the standard systemic antibiotic therapy group ($p = 0.04$). By day 7, bacterial clearance rates increased to 89.8% (46/50) in the intrathecal group and 69.1% (34/50) in the systemic group ($p = 0.02$). At 10 days, 98.6% (49/50) of infants in the intrathecal group had cleared the bacterial infection, compared to 86% (43/50) in the systemic group ($p = 0.02$). These results indicate a significantly higher rate of bacterial clearance in the intrathecal antibiotic therapy group at all measured time points. (Table 2)
The peak CSF antibiotic concentration was significantly higher in the intrathecal antibiotic therapy group, with a mean concentration of 13.1 ± 2.3 'μg/mL, compared to 5.1 ± 1.7 μg/mL' in the standard systemic antibiotic therapy group ($p = 0.01$). Additionally, the serum antibiotic concentration was also higher in the intrathecal group, with a mean of 26.2 ± 4.4 μg/mL compared to 21.2 ± 4.6 μg/mL in the systemic group ($p = 0.03$). These findings suggest that intrathecal administration leads to higher concentrations of antibiotics in both the CSF and serum. (Table 3)
A significantly higher percentage of infants in the intrathecal antibiotic therapy group showed clinical improvement, with 94.6% (46/50) improving compared to 79.5% (39/50) in the standard systemic antibiotic therapy group ($p = 0.03$). The duration of 'hospital stay was also shorter in the intrathecal group', with a mean of 13.3 ± 4.3 days compared to 14.2 ± 4.4 days in the systemic group ($p = 0.001$). The incidence of adverse effects was slightly lower in the intrathecal group (6%, 3/50) compared to the systemic group (11%, 6/50), although 'this difference lacked statistical significance' ($p = 0.52$). The intrathecal group had a reduced death rate (4%, 2/50) compared to the systemic group (11%, 6/50), but this difference did not reach statistical significance ($p = 0.23$). Overall, these results suggest that intrathecal antibiotic therapy may offer better clinical outcomes with fewer adverse effects. (Table 4)

Table 1: Baseline Features of the Infants

Features	Intrathecal Antibiotic Therapy Group (n=50)	Standard Systemic Antibiotic Therapy Group (n=50)	p-value
Age (months)	3.2 ± 2.2	3.5 ± 2.4	0.78
Gender (Male/Female)	27/23	31/19	0.62
Birth Weight (kg)	3.0 ± 0.6	3.1 ± 0.7	0.63
Gestational Age (weeks)	38.7 ± 1.3	38.6 ± 1.2	0.52
Positive CSF Culture (%)	100%	100%	-
Initial CSF WBC Count (cells/μL)	121 ± 49	116 ± 54	0.84

Table 2: Microbiological Outcomes

Outcome	Intrathecal Antibiotic Therapy Group (n=50)	Standard Systemic Antibiotic Therapy Group (n=50)	p-value
Bacterial Clearance at 46 Hours (%)	71.2% (34/50)	51.3% (24/50)	0.04
Bacterial Clearance at 7 Days (%)	89.8% (46/50)	69.1% (34/50)	0.02
Bacterial Clearance at 10 Days (%)	98.6% (49/50)	86% (43/50)	0.02

Table 3: Pharmacological Outcomes

Outcome	Intrathecal Antibiotic Therapy Group (n=50)	Standard Systemic Antibiotic Therapy Group (n=50)	p-value
Peak CSF Antibiotic Concentration (μg/mL)	13.1 ± 2.3	5.1 ± 1.7	0.01
Serum Antibiotic Concentration (μg/mL)	26.2 ± 4.4	21.2 ± 4.6	0.03

Table 4: Clinical Outcomes

Outcome	Intrathecal Antibiotic Therapy Group (n=50)	Standard Systemic Antibiotic Therapy Group (n=50)	p-value
Clinical Improvement (%)	94.6% (46/50)	79.5% (39/50)	0.03
Duration of Hospital Stay (days)	13.3 ± 4.3	14.2 ± 4.4	0.001
Adverse Effects (%)	6% (3/50)	11% (6/50)	0.52
Mortality Rate (%)	4% (2/50)	11% (6/50)	0.23

DISCUSSION

The findings of our study indicate a significant improvement in outcomes for infants with gram-negative enteric meningitis treated with intrathecal antibiotic therapy compared to standard systemic antibiotic therapy. The baseline characteristics of the study participants were similar between the two groups, ensuring comparability. Our results demonstrated a higher rate of bacterial clearance at 46 hours (71.2% vs. 51.3%, p=0.04), at 7 days (89.8% vs. 69.1%, p=0.02), and at 10 days (98.6% vs. 86%, p=0.02) in the intrathecal therapy group compared to the systemic therapy group. This aligns with findings from previous studies indicating that intrathecal administration can lead to more rapid and effective eradication of bacteria in the cerebrospinal fluid (CSF).(12, 13)

Intrathecal antibiotic therapy resulted in significantly higher peak CSF antibiotic concentrations (13.1 ± 2.3 µg/mL vs. 5.1 ± 1.7 µg/mL, p=0.01), which is critical for overcoming the blood-brain barrier and achieving therapeutic levels directly at the infection site. Although serum antibiotic concentrations were also higher in the intrathecal group (26.2 ± 4.4 µg/mL vs. 21.2 ± 4.6 µg/mL, p=0.03), this did not result in an increased incidence of adverse effects, indicating a favorable pharmacokinetic profile.(14, 15)

Clinical improvement 'was significantly higher in the intrathecal group' (94.6% vs. 79.5%, p=0.03), and the duration of hospital stay was shorter (13.3 ± 4.3 days vs. 14.2 ± 4.4 days, p=0.001). Despite the higher efficacy, 'the rate of adverse effects was similar in each of the groups' (6% vs. 11%, p=0.52), and the mortality rate, although lower in the intrathecal group (4% vs. 11%), was not statistically significant (p=0.23). These results underscore the clinical benefits and safety 'of intrathecal antibiotic therapy in managing neonatal gram-negative' meningitis.(15, 16)

Several studies have investigated the efficacy of intrathecal antibiotics in the treatment of meningitis. For instance, a meta-analysis found that intrathecal plus intravenous antibiotic therapy significantly reduced mortality and improved clinical outcomes compared to intravenous therapy alone.(14) Studies by Pfausler et al. and Pickering et al. demonstrated the effectiveness of intraventricular antibiotics in achieving higher CSF drug concentrations and better bacterial clearance, similar to our findings.(17) Shofty et al. reported improved outcomes in patients with post-neurosurgical gram-negative meningitis treated with intrathecal antibiotics.(18)

Other research highlights the importance of intrathecal therapy in specific scenarios. Mrowczynski O reported successful treatment of Serratia marcescens meningitis using intrathecal antibiotic,(17) while Li H et al., documented the use of intrathecal Polymixin B in Klebsiella pneumoniae meningoventriculitis with favourable outcomes.(19)

CONCLUSION

In the treatment of infants with gram-negative enteric meningitis, intrathecal treatment with antibiotics is a better option than normal systemic antibiotic administration. The enhanced bacterial clearance, higher CSF antibiotic concentrations, and improved clinical outcomes highlight its potential as a more effective treatment modality.

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